specification as that appearing in US Patent 6,011,259, and reference to the '259 patent has been made in the identified table.

While there may be some minor editorial changes to the table, the details presented in that table are applicable to the present rejection. Additionally, further presentations will be made in response to the interview conducted on December 9, 2003 when Examiner Kiet T. Nguyen graciously conducted an extended interview with the undersigned, as well as Craig Whitehouse, one of the co-inventors, and Dr. David Welkie, another employee of the Assignee of the current application.

The rejection of November 19, 2003 states the Examiner's positions that the limitations in the subparagraphs of the proposed counts were not supported by the specification or related applications. But the Examiner's positions were not detailed. Unfortunately, the point by point analysis presented in the prior response of July 23, 2003 was neither addressed in the Office Action of November 19th nor was it discussed in detail.

On the other hand, it appeared that during the interview Craig Whitehouse explained to Examiner Nguyen with sufficient clarity why the specific limitations which were generally objected to in the Office Action of November 19, 2003 should be withdrawn in view of the detailed presentations contained in the current application, its predecessor, 6,011,259, and related patent 5,689,111.

First and foremost, the subject matter of the instant invention and that of 6,285,027 is the same. The inventions concern conducting MS/MSn analysis using a Time-of-Flight mass analyzer and has been described in detail in the referenced tables and will be discussed in greater detail below.

The present invention includes a multipole ion guide incorporated in either a coaxial or orthogonally pulsed API/TOF mass analyzer instrument. This multipole ion guide can be operated in either a mass filter, a transmission, trapping or ion fragmentation mode to increase sensitivity and provide MS/MSn capability with TOF analyzers.

The Examiner has objected to the fact that there is not an identicality of English word usage between the 6,285,027 and that of the current pending application. It is noted that the attorneys who wrote and prosecuted 6,285,027 are from Canada. To the extent that that application and resulting patent was written and prosecuted by Canadian patent

attorneys who have a slightly different usage of English languag words, there might be some difference in use of words to describe the same structure, function and method. Beyond that basis for there being any literal word differentiation, the inventions are the same.

Turning now in detail to the rejection contained in the Office Action of November 19, 2003, the Examiner stated:

> "The specification is completely silent for reciting the limitations 'subjecting the parent ions to collision induced disassociation to generate fragment ions' as recited in step b of claims 99 and 115."

Table 1 clearly identifies, at a minimum, specification support. On the other hand, it is hard to understand how one could read US Patent 6,011,259 (which has the same specification as the current application) and not readily and repeatedly see that the invention deals with trapping fragment ions and any remaining parent ions. Column 8, lines 1-7 state:

> "The multipole ion guide is configured to operate with m/z range selection, trapping and subsequent ion fragmentation using CID within the multipole ion guide. Parent ions and multiple generations of fragment ions formed within the ion guide are subsequently Time-Of-Flight mass analyzed."

Column 9, lines 19-21 state:

> "The invention includes at least three methods to perform ion fragmentation with CID in the linear multipole ion guide."

Column 11, lines 31-35, state:

> "As will be described in a later section, increasing the internal energy of ions from the capillary skimmer region can be used to advantage when fragmenting ions within the ion guide using CID of ions with the background gas in the multiple ion guide."

Next the Examiner claimed that the specification was completely silent for reciting the limitation "trapping the fragment ions and any remaining parent ions" as recited in step c. Here again, it is believed that that rejection has been withdrawn since specifics relating to support in the specification were contained in table 1 previously submitted and was

discussed during the interview. Further, the specification of 6,011,259 is replete with continuing discussions of the trapping of fragment ions and parent ions, all as part of the MS/MSn analysis. There are numerous variations relating to how to alter the trapping of the fragment and any remaining parent ions throughout the specification, and additional reference to several of those will be hereinafter made.

As specifically stated in the table, reference to column 9, lines 1-9, identifies the following: "All or a portion of the trapped ions are then transmitted to the pulsing region of the TOF mass analyzer where they are accelerated into the TOF flight tube and m/z analyzed." As stated in the table, it is understood to one of ordinary skill in the art that fragmenting: "All or a portion" of the ions produces both parent and fragment or daughter ions in the same space. The fact that the specification may not use the specific words "any remaining parent ions" is not believed to be a deficiency since one skilled in the art would understand that those words directly applied to: "All or a portion of the trapped ions."

Further, as is known to one of ordinary skill, there will always be remaining parent ions trapped with the fragment ions after CID no matter how sensitive the filtering may be. Thus, the statement trapping the fragment ions and any remaining parent ions is really stating "trapping the 'ions'", since the ions that are trapped after CID include both fragment and parent ions.

Further, it is noted on column 19, lines 51-66, that steps 4, 5 and 6 directly relate to and support the fact that fragment ions and remaining parent ions are trapped (see specifically step 5 in conjunction with steps 4 and 6). Again, with the steps listed at the bottom of paragraph 20 on to the top of column 21, step 4 repeats that fragments ions are produced in the ion guide trap from the remaining trapped parent ions.

Next, the Examiner also states that the specification is completely silent for reciting the limitation "periodically releasing pulses of the trapped ions into a Time-Of-Flight instrument" as recited in step d. Here again, reference is made to the previously submitted table. Further, additional identification in the specification of the '259 patent will be made.

Referencing the periodic releasing of the pulses, please refer to column 14, lines 14, et seq.: "This is accomplished by controlling the length of ion packet 52 and timing the release of ion packet 52 from ion guide 16 with the TOF pulse of lenses 34 and 35. A time

separated m/z ion packet consisting of subpackets 54 and 56 just befor the TOF ion pulse occurs is diagramed in Figure 3."

Further down, beginning on column 14, line 30: "The ion fill level of multipole ion guide 16 operated in trapping mode is controlled by the ion fill rate, stable m/z range selected, the empty rate set by the ion guide ion release TOF pulse event and the TOF pulse repetition rate."

Column 18, line 57, et seq.: "Five individual TOF mass spectra were summoned to produce each mass spectra shown in Fig. 8. Hence a total of 25 microseconds of ion guide trap empty time was required to produce each parent and first generation fragment ion mass spectra 80, 81 and 82 respectively. Similar, ion signal levels were obtained for ions trapped in ion guide 80 over a ion release period exceeding 200 microseconds. Consequently, several summed TOF mass spectra can be produced from one set of ions trapped at ion guide 60."

Column 23, line 14, et seq.: "Only a short duration ion release pulse from ion guide 60 can be used with the co-linear TOF pulsing geometry. Increasing the duration of the ion release pulse from ion guide 60 decreases TOF analysis resolution."

Thus, there is ample support for "periodically releasing pulses by the trapped ions into a TOF."

Next the Examiner states the specification is completely silent for reciting the limitation "providing a delay between the release of pulses of trapped ions and initiation of pulses in the TOF and adjusting the delay ..... charge ratio" as recited in step e.

Column 12, line 63 through column 13, line 2: "Due to constraints imposed by circuitry, factors of only 2 to 4 can be gained by increasing the TOF pulse rate above 10 kHz, consequently, m/z 500 may only achieve a maximum duty cycle of 28% in continuous beam operating mode. Instead, trapping and the timed release of ions from the multipole ion guide is a preferred method of improving the duty cycle."

Column 14, line 14, et seq.: "This is accomplished by controlling the length of ion packet 52 and timing the release of ion packet 52 from ion guide 16 with the TOF pulse of lenses 34 and 35."

The empty rate set by the ion guide ion release, which releases ions into the TOF is the adjustment of the delay to improve the duty cycle efficiency. Further, as identified above in reference to column 12, line 63 through column 13, line 2.

Again, on column 15, line 45, et seq.: "Very high duty cycle can be maintained in ion guide trapping mode with lower TOF pulse repetition rates."

Further, on column 15, line 66, et seq.: "If just the second generation fragment mass spectrum were desired, the acquisition of only two mass spectra would be required for subtraction and hence the duty cycle is only one half of the optimal parent ion trapping mode of operation. If the fragmentation sequence is desired for MS/MS_2 acquisition of the duty cycle of the second generation fragment ion mass spectrum would be one third that of the optimal parent ion trapping mode of operation as three sum mass spectra would be acquired. Clearly this resonant frequency CID technique using a multipole ion guide with single or multiple resonant frequency CID can be extended to perform high duty cycle MS/MSn analysis."

Column 18, lines 2-16 describe two different ion guide fill times which relates to release of the pulses of trapped ions into the TOF instrument and adjustment of the timing to improve the duty cycle efficiency.

Column 23, lines 27, et seq.: "Consequently, the relative m/z ion population of a TOF ion packet pulsed on flight tube 70 may differ from the relative m/z ion population trapped in ion guide 60 when short duration ion release pulses are used. Also with the constraint that only short duration release pulses can be used to extract ions from ion guide 60, the level of ion guide filling is more difficult to control without shutting off the primary beam. Interrupting the primary beam reduces the effective duty cycle."

While the above submission references the previously submitted table and submissions, the following reiterates and presents in even more detail further analysis underlining the clear connection between the invention herein, that of the '027 patent and claim 1 which is the count.

Background

The Sciex '027 patent, comprising Claims 1-6, claims methods for MS/MS analysis of ions. We contend that these methods were described previously in the description of the AOB '259 patent, especially when considered in conjunction with AOB patent '111 (which was incorporated in '259 by reference), thereby requiring that an interference be declared.

At present, we focus on '027 Claim 1, which we present as Count 1, and argue that support for this claim language is found in the '259 description, and this support is even stronger by inclusion of '111 patents.

Count 1 reads:

1. A method of effecting mass analysis on an ion stream, the method comprising:

(a) passing the ion stream through a first mass resolving spectrometer, to select parent ions having a first desired mass-to-charge ratio;

(b) subjecting the parent ions to collision-induced dissociation to generate fragment ions;

(c) trapping the fragment ions and any remaining parent ions;

(d) periodically releasing pulses of the trapped ions into a time of flight instrument to detect ions with a second mass-to-charge ratio; and

(e) providing a delay between the release of the pulses of trapped ions and initiation of push-pull pulses in the time of flight instrument, and adjusting the delay to improve the duty cycle efficiency of ions with the second mass-to-charge ratio.

Count 1 identifies a method for MS/MS analysis whereby: (a) particular ions (the "parent ions" with a first mass-to-charge ratio) are first selected via an "MS" step. The selected parent ions are then (b) fragmented via collision-induced dissociation. At this point, the method is entirely conventional as the Examiner knows. To complete the steps necessary for well-known *conventional* MS/MS analysis, the fragment ions and any remaining parent ions would typically then be subjected to a second mass-to-charge analysis step to detect ions with a second mass-to-charge ratio.

It is well-known in the prior art to perform this second mass analysis step with a quadrupole mass filter, such as in a so-called 'triple-quadrupole' configuration as the Examiner knows. However, the latter three method steps of Count 1 describe the use of a time-of-flight mass spectrometer for performing this second mass analysis, specifically, by: (c) trapping these ions; (d) periodically releasing at least some of them into a time-of-flight analyzer for mass-to-charge analysis; and (e) providing a delay between this pulsed ion release and the TOF acceleration pulse, where the delay is adjusted to improve duty cycle (sensitivity) for ions with a second mass-to-charge ratio.

These latter three method steps are described in the AOB '111 patent for MS analysis of *parent* ions with a TOF MS. The claimed novelty then seems to boil down to the application of these three steps for *fragment* ions (and any remaining parent ions) previously created by collision-induced dissocation.

Even though the Examiner had no specific objection in the Office Action of November 19, 2003 to step (a), step (a) will be included in this reply, not only to support that the order of the steps are taught in the '259 description, but also because the Examiner seemed to have an issue during our interview regarding the word "through" in step (a). Specifically, the Examiner seemed not to be clear about how the apparatus of '259 performs the steps of Count 1 while satisfying the Examiner's interpretation of the meaning of the word "through", so this issue is addressed below.

Detailed Discussion

It appears that clear support for each step of Count 1, as well as their order, is contained in '259, Col. 16, lines 34-67 through Col. 17, lines 1-40; all of Col. 13, and Col. 14, lines 1-36. Details are presented below for each step.

A. Support for step (a) 'passing the ion stream through a first mass resolving spectrometer, to select parent ions having a first desired mass-to-charge ratio', is contained in:

> Column 16, line 34, et seq.: "With the embodiment of the invention as diagrammed in FIG. 1, *an MS/MS experiment includes the steps of m/z selection* and accumulation in ion guide 16 operating in trapping mode followed by an ion

> fragmentation step. *Initially*, in an MS/MS experiment, *the primary ion beam is turned on and ions enter ion guide 16 which is operating in m/z selection mode. As described above, mass or m/z selection in ion guide 16 can achieved in a number of ways.*"

In other words, '*...the primary ion beam is turned on and ions enter ion guide 16 which is operating in m/z selection mode...*' in '259 equates to the act of 'passing the ion stream through a first mass resolving spectrometer' of step (a). Also, the function part of step (a), 'to select parent ions having a first desired mass-to-charge ratio' is described by '*...includes the steps of m/z selection*'.

There appeared to be an issue during the interview with the Examiner in December, 2003, regarding the word 'through' in step (a). The first two definitions of the word 'through' in the Thorndike-Barnhart dictionary are: 1. from end to end of; from side to side of; between the parts of; from beginning to end of: *march through a town, cut a tunnel through a mountain.* 2. here and there in; over; around: *stroll through the streets of a city.* Taking the first definition of 'through' would imply that ions exit the mass spectrometer as part of step (a), while applying the second definition would imply that ions only need pass through a portion of the spectrometer as part of step (a), and need not exit. Hence, the meaning of the word through in step (a) covers both definitions (1) and (2) above literally and actually.

Interpretation of the word 'through' according to the second definition is all that is required in order to execute the function of step (a) of selecting parent ions. To 'select', that is, to chose to the exclusion of all others, ions with a particular m/z ratio need to be isolated, either spatially or temporally, from all others in any mass resolving spectrometer before the ions exit the spectrometer, if, in fact, the Ions exit at all. In other words, exiting the mass spectrometer is not necessary for the 'selection' of Ions of a particular mass-to-charge ratio. Therefore, the language of step (a) encompasses either situation of selecting 'parent ions having a first desired mass-to-charge ratio', that is: 1) passing the ion stream partly through or within the mass spectrometer and then allowing selected ions to exit; and 2) just passing the ion stream partly through the mass spectrometer.

It is important to note that step (a) does not require that ions go from end to end or completely through since the language is not so limited.

Nevertheless, the '259 description discloses different implementations of step (a) which support both interpretations of the word 'through'. In one approach disclosed in the '259 description, 'selected' ions do, in fact, exit the ion guide mass spectrometer prior to the next step of fragmentation, as described in Col. 17, lines 1-12:

> "...such that ions leaving ion guide exit 24 move to fill the gap between lenses 26 and 27. When the gap between lenses 26 and 27 is filled, the voltages on lenses 26 and 27 are rapidly increased effectively changing the energy of ions in the gap between the end of rods 20 and lens 27. The relative voltages on the lenses 26 and 27 and the offset potential of ion guide 20 are set such that the ions sitting at a raised potential are accelerated back into the exit end 24 of ion guide 16 and travel from ion guide exit end 24 toward ion guide entrance end 60 through the length of the internal volume of ion guide 16 colliding with neutral background molecules in a portion of the ion guide length."

Thus, selected ions exit the mass resolving spectrometer (ion guide) and are then accelerated back into the ion guide, which contains gas molecules with which the ions collide and fragment by CID. This process is identical to the description of mass selection and fragmentation given in '027, except that 'selected' ions having exited the mass resolving spectrometer are accelerated in the *downstream* direction to an ion guide with gas molecules to cause CID, while in '259, 'selected' ions having exited the mass resolving spectrometer are accelerated in the *upstream* direction to an ion guide with gas molecules to cause CID.

Alternatively, in another scenario, the '259 description discloses 'passing the ion stream through a first mass resolving spectrometer, to select parent ions having a first desired mass-to-charge ratio' without the selected ions exiting the mass spectrometer before the next step of fragmentation takes place. This is described by the passage in the beginning of this section A.

In any case, it appears that there is ample support for step (a) in the '259 description.

B. Support for step (b), 'subjecting the parent ions to collision-induced dissociation to generate fragment ions', is also included in the above passage, specifically in lines 34-38 "...*an MS/MS experiment includes the steps of m/z selection ... followed by an ion fragmentation step*". Note explicit definition of the order of these steps. The ion fragmentation step is subsequently described in more detail in Col. 16, lines 53-67 and Col. 17, lines 1-12. First, Col. 16, lines 53-60 reads:

> "*Fragmentation of trapped ions in ion guide 16* can be achieved by using one of at least three techniques. The first technique as was described above for continuous beam operation is to apply a resonant frequency to rods 20 of ion guide 16 to cause resonant excitation *of all or a portion of the trapped ions*. The resonant excitation results in fragmentation *due to CID of the translationally excited ions with the background gas in ion guide 16*."

Because "*Fragmentation of trapped ions in ion guide 16...*" above refers to the m/z selected ions from step (a) which are then subjected to a fragmentation step, the trapped ions are the same as the 'parent ions' of Count 1, step (b). Therefore, "*Fragmentation of trapped ions in ion guide 16... of all or a portion of the trapped ions...due to CID of the translationally excited ions with the background gas in ion guide 16*", in the '259 description, is the same as 'subjecting the parent ions to collision-induced dissociation to generate fragment ions' of step (b).

The above passage describes one embodiment of this step, that is, resonant frequency excitation fragmentation of parent ions while they are trapped in the ion guide. Obviously, any fragment ions so produced are also trapped in the ion guide.

A second method of achieving CID fragmentation of m/z selected parent ions is described in the immediately following passage, Col. 16, lines 61-67 through Col. 17, lines 1-12:

> "A second technique and another aspect of the invention allows higher energy fragmentation to occur than can be achieved with resonant frequency CID. This second ion fragmentation technique is realized by switching the offset potential of ion guide 16 and the voltage applied to lens 26 to

> release ions trapped in ion guide 16 and accelerating them at higher energy back into exit end 24. A short release pulse is used such that ions leaving ion guide exit 24 move to fill the gap between lenses 26 and 27. When the gap between lenses 26 and 27 is filled, the voltages on lenses 26 and 27 are rapidly increased effectively changing the energy of ions in the gap between the end of rods 20 and lens 27. The relative voltages on the lenses 26 and 27 and the offset potential of ion guide 20 are set such that the ions sitting at a raised potential are accelerated back into the exit end 24 of ion guide 16 and travel from ion guide exit end 24 toward ion guide entrance end 60 through the length of the internal volume of ion guide 16 colliding with neutral background molecules in a portion of the ion guide length."

Essentially, as described previously in section A., m/z selected parent ions are allowed to pass completely through the ion guide and out the exit end of the ion guide. Then voltages applied to the exit lens components are switched such that the ions are turned around and accelerated back into the ion guide, where they ultimately encounter gas molecules in the ion guide, and collisions with the gas molecules result in fragmentation of the ions by CID.

Thus, there appears to be ample support for step (b), as well as its proper order of execution, in the '259 description.

Further, regarding the order of execution of the steps of Count 1: During the meeting with the examiner a specific portion of the text in the '259 patent were pointed out to address his question of support for order of events as cited in the claim. The listed and numbered steps 1 through 8 in column 19, lines 55 through 67 and column 20, lines 1 and 2 describe in detail an MS/MS experiment with Trappulse TOF analysis conducted in the precise order as stated in the claims. The Examiner reviewed this passage during the interview with him and he raised no questions or objections.

Also during the interview with the Examiner, the examiner was focused on m/z selected parent ions being accelerated from one ion guide to a second ion guide to cause CID fragmentation. In column 21, lines 26 through 67 and column 22, lines 1 through 27 the description of the two ion guide embodiment diagrammed in Figure 4 is given where m/z ion selection occurs in ion guide 111 and m/z selected parent ions are reverse

accelerated into ion guide 110 (column 22, lines 4 through 13) to cause ion collision induced fragmentation with both ion guides operating in trapping mode. The examiner accepted that the reverse accelerating ions from one ion guide to a second ion guide was a valid method of conducting CID and MS/MS^n analysis creating the same fragment ion population as would result from forward acceleration of ions from one ion guide to a second ion guide with ion CID occurring in the second ion guide.

C. Support for step (c), 'trapping the fragment ions and any remaining parent ions' is found in the passage quoted above for the first embodiment of the fragmentation step, that is, Col. 16, lines 53-60,

> "*Fragmentation of trapped ions in ion guide 16* can be achieved by using one of at least three techniques. The first technique as was described above for continuous beam operation is to apply a resonant frequency to rods 20 of ion guide 16 to cause resonant excitation *of all or a portion of the trapped ions*. The resonant excitation results in fragmentation *due to CID of the translationally excited ions with the background gas in ion guide 16.*"

This passage describes the ion guide being operated as an ion trap, trapping parent ions while subjecting them to CID fragmentation by resonant frequency excitation. It is well known in the art that the formation of fragment ions while trapping parent ions will result in the fragment ions being trapped as well. Also, as the '259 description makes explicit in Col. 16, lines 57-58, "...to cause resonant excitation *of all or a portion of the trapped ions*...", allows that, after the fragmentation step, the ion population trapped in the ion guide could consist of 'fragment ions and any remaining parent ions', as specified in step (c). Hence, step (c) is robustly described in '259, and in the order specified by Count 1.

Further support for step (c) is found in conjunction with the description of the second method of fragmentation discussed above. Following the description of the reverse-acceleration method of fragmentation described above in Col. 16, lines 61-67 through Col. 17, lines 1-12, the passage continues at Col. 17, lines 12-18:

> "The ions traversing ion guide 16 in the reverse direction are prevented from leaving entrance end 60 of ion guide 16 by setting the appropriate retarding potential on skimmer 14.

> *During this step where ions are accelerated back into ion guide exit 24*, the ion guide offset potential and the voltage on lens 26 are set such that *ions within the ion guide remain trapped.*"

And the passage continues at Col. 17, lines 26-31:

> "This ion reverse direction acceleration step can be repeated a few or several times *to fragment a portion or all of the parent ions trapped in the ion guide*. This repetitive reverse direction acceleration step can also cause *additional fragmentation of fragment ions* provided the collision energies are sufficient."

These passages specify that ions are trapped in the ion guide, that all or a portion of parent ions may be fragmented, and that fragment ions are also trapped (otherwise '*additional fragmentation of fragment ions*' would not make sense).

Hence, support for step (c), 'trapping the fragment ions and any remaining parent ions' seems clear because of any of the above three independent bases.

D. Support for step (d), 'periodically releasing pulses of the trapped ions into a time of flight instrument to detect ions with a second mass-to-charge ratio' is found in passages that immediately follow the latter quoted passage, that is, in Col. 17, lines 31-40:

> "*After sufficient ion fragmentation has occurred* by this method, *a series of TOF mass spectra can be acquired of the ion population trapped in ion guide 16.* As was described in an earlier section, *releasing of trapped ions from ion guide 16 for TOF mass analysis followed by trapping of the ions remaining in ion guide* 16, can be achieved either by changing the voltages on just lens 26 or conversely, the ion guide offset potential, skimmer 14 voltage and the voltage on capillary exit 12 can be stepped together."

This passage identifies that the next step after fragmentation is *to acquire a series of TOF spectra of the ions trapped in the ion guide*. The '*ions trapped in the ion guide*' are obviously the fragment ions and any remaining parent ions from step (c). '*A series of TOF spectra can be acquired*' (of these ions) identifies that this step (d) entails acquisition of a plurality ('*a series*') of TOF mass spectra of these ions, which inherently involves detection of ions with more than one mass-to-charge values, hence, certainly involves the detection

of 'ions with a second mass-to-charge value' as specified in step (d). Further, *'releasing of trapped ions from ion guide 16 for TOF mass analysis followed by trapping of the ions remaining in ion guide* 16' is the same as to 'periodically releasing pulses of the trapped ions into a time of flight instrument', in step (d). This equivalence is more explicit in the detailed description in the earlier section referred to in this passage for the releasing of some trapped ions for TOF analysis and trapping of remaining ions. This earlier section is Col. 13, lines 3-67 through Col. 14, lines 1-29. Of particular relevance to step (d) is an excerpt from this passage, Col. 13, lines 62-66:

> "By either trapping method, ions continuously enter ion guide 16 even while *packets are being pulsed out exit end 24. The time duration of the ion release from ion guide exit 24 will create an ion packet 52 of a given length as diagrammed in Fig. 2.*"

Hence, the '259 description describes packets (of ions) being pulsed out exit end 24 (of the ion guide trap), in other words, 'periodically releasing pulses of the trapped ions', as expressed in step (d). Therefore, support for step (d), 'periodically releasing pulses of the trapped ions into a time of flight instrument to detect ions with a second mass-to-charge ratio', in the '259 description, as well as for the sequence that step (d) follows step (c), is clear.

E. Step (e) is 'providing a delay between the release of the pulses of trapped ions and initiation of push-pull pulses in the time of flight instrument, and adjusting the delay to improve the duty cycle efficiency of ions with the second mass-to-charge ratio'.

Again, ample support for this step is found in the '259 description and U.S. Patent Number 5,689,111 incorporated into '259 by reference. First, however, it is necessary to clarify what is meant by 'push-pull' pulses. This is simply a term that refers the pulsed acceleration field that is turned on abruptly in order to accelerate ions in the TOF upon initiation of a TOF spectrum measurement. It is a term that is considered well-known to those familiar with the art of time-of-flight mass spectrometers. Indeed, the '027 specification uses this terminology without explanation or definition, for example, in Col. 5, lines 58-61: "Grids 36 are provided in known manner for effecting a push-pull pulse to

ions collected in the ion storage zone 34.", and, in Col. 6, lines 35-37, "Line 74 shows the variation of potential of the conventional push-pull arrangement at the ion collection zone 34." Hence, it may be stated that the term 'push-pull pulses' is generally understood to be synonymous with simply "TOF pulses" as used in the '259 description. (See, e.g., Col. 14, line 16 and line 33.)

Support for step (e) is found initially in the '259 description in Col. 12, line 67 through Col. 13, lines 2:

> "Instead, *trapping and the timed release of ions* from the multipole ion guide *is a preferred method for improving duty cycle*."

This teaching introduces the concept of improving the duty cycle by a process of trapping ions and properly timing their release to the TOF. This concept is elaborated on, following a detailed discussion of different ways of performing the trapping step, in subsequent passage of Col. 13, lines 62-67 through Col. 14, lines 1-29:

> "By either trapping method, ions continuously enter ion guide 16 even while ion packets are being pulsed out exit end 24. The time duration of the ion release from ion guide exit 24 will create *an ion packet 52 of a given length* as diagrammed FIG. 2. As *this ion packet moves through lenses 27 and into pulsing region 30 some m/z TOF partitioning can occur* as diagrammed in FIG. 3. The m/z components of ion packet 52 can occupy different axial locations in pulsing region 30 such as separated ion packets 54 and 56 along the primary ion beam axis. Separation has occurred due to the velocity differences of ions of different m/z values having the same energy. The degree of m/z ion packet separation is in part a function of the initial pulse duration. The longer the time duration that ions are released from exit 24 of ion guide 16, the less m/z separation that will occur in pulsing region 30. *All or a portion of ion packet 52 may fit into the sweet spot of pulsing region 30. Ions pulsed from the sweet spot in pulsing region 30 will impinge on the surface of detector 38.* If desired, a reduced m/z range can be pulsed down flight tube 42 from pulsing region 30. This is accomplished by controlling the length of ion packet 52 and *timing the release of ion packet 52 from ion guide 16 with the TOF pulse of lenses 34 and 35. A time separated m/z ion packet consisting of subpackets 54 and 56 just before the TOF ion pulse occurs is diagramed in FIG.*

> 3. Ion subpacket 56 of lower m/z value has moved outside the sweet spot and will not hit the detector when accelerated down flight tube 42. Ion subpackets 57, originally subpackets 54, are shown just after the TOF ion pulse occurs. These subpackets will successfully impinge on detector 38. The longer the initial ion packet 52 the less mass range reduction can be achieved in pulsing region 30. *With ion trapping in ion guide 16, high duty cycles can be achieved* and some degree of m/z range control in TOF analysis can be achieved independent or complementary to mass range selection operation with ion guide 16."

This passage first describes a pulse, or packet, of ions of a given length (depending on the trap pulse duration) being pulsed out of the ion guide trap. Then, "*As this ion packet moves through lenses 27 and into pulsing region 30 some m/z TOF partitioning can occur...*". In other words, it takes some time for the pulsed ion packet to travel from the ion guide trap to the pulsing region of the TOF, and, obviously, the TOF push-pull pulse would not be activated until the ion packet, or some portion of the packet, has arrived within the TOF 'sweet spot', that is, the region within the TOF pulse region from which ions are able to reach the TOF detector once the TOF pulse occurs. This time delay is expressed explicitly in this passage by "*...timing the release of ion packet 52 from ion guide 16 with the TOF pulse of lenses 34 and 35. A time separated m/z ion packet consisting of subpackets 54 and 56 just before the TOF ion pulse occurs is diagramed in FIG. 3.*" Clearly, '...timing the release of ion packet...with the TOF pulse...' is the same as 'providing a delay between the trap release of the pulses of trapped ions and the initiation of push-pull pulses in the time of flight instrument.'. Such a delay is even more explicitly described in the '111 description, as discussed below.

The second part of step (e) is '...and adjusting the delay to improve the duty cycle efficiency of ions with the second mass-to-charge ratio'. The passage from '259 quoted above includes the statements: "*All or a portion of ion packet 52 may fit into the sweet spot of pulsing region 30. Ions pulsed from the sweet spot in pulsing region 30 will impinge on the surface of detector 38.*" In other words, this passage teaches that all ions of an ion packet may be detected in the TOF, provided that they are located within the sweet spot of the TOF pulsing region at the time that the TOF pulse occurs. Now, obviously, all ions

of an ion packet of a particular mass-to-charge ratio will be located within the sweet spot of the TOF pulsing region only if the timing of the TOF pulse occurs after a particular time delay relative to the ion guide trap release pulse. Hence, it would seem to be clear that this passage supports the second part of step (e) '... adjusting the delay to improve the duty cycle efficiency of ions with the second mass-to-charge ratio'.

The above arguments for support for step (e) in the '259 specification are further bolstered by considering the incorporation by reference of then co-pending patent application, now issued U.S. patent # 5,689,111, which describes in explicit detail the pulsed release of ions from an ion guide trap, and the improvement in duty cycle of an ion with a particular mass-to-charge ratio by adjusting the delay between the release of the pulses of trapped ions and initiation of TOF pulses. In the '111 description, Col. 8, lines 1-28 read:

> "As an example to the ion storage mode of operation, let us again use the same mixture of ions M1, M2, and M3 of ionic masses 997, 508 and 118 as used above in continuous mode of operation. As shown in FIG. 4, and FIG. 6 the pulsed ion beam of duration t1 from the region 72 is injected between the parallel plates 23 and 24 when the plates are initially held at the absence of an electric field, i.e. voltage level 79 on the repeller lens 23. According to the above equation (3), lighter ions moving faster than the heavier ions, the three masses will start to separate from each other in the region 26. *After a certain variable delay t2, the electric field in the region 26 is pulsed on* for a short period of time t3 by the repeller plate 23. The *delay time t2 can be changed to allow* different sections of the original ion beam, i.e. *different m/z packages*, to accelerate perpendicular to their original direction towards the flight tube 35 *to be detected for mass analysis*. In this example, *a delay time t2 was chosen to pulse only a narrow range of ions centered around mass (M2) 53* which were accelerated in the direction 63 at the instant the field was turned on. At the same instant, both the masses M1 52 and M3 54 will hit the sides of the lenses moving in the approximate direction 62 and 64 and will not be detected by the mass analyzer."

This passage clearly describes 'providing a delay (i.e., t2) between the release of the pulses of trapped ions and initiation of push-pull pulses in the time of flight instrument,' in the passage "*After a certain variable delay t2, the electric field in the region 26 is pulsed*

on" , while 'and adjusting th delay to improve the duty cycle fficiency of ions with the second mass-to-charge ratio' is described by "*..delay time t2 can be changed to allow.. different m/z packages.. to be detected for mass analysis.. a delay time t2 was chosen to pulse only a narrow range of ions centered around mass (M2) 53...*". The resulting improvement in the duty cycle is demonstrated in the subsequent description of demonstrated experimental results in Col. 8, lines 44-67 through Col 9, lines 1-16, which read:

> "*FIGS. 7A and 7B show the actual experimental results* acquired using both the continuous and ion storage mode of operations for a sample using a mixture of ions used in the above examples. The actual sample was a mixture of three compounds Valine, tri-tyrosine, and hexa-tyrosine. Upon electrospray ionization of this mixture, the predominant molecular ions with nominal masses 118, 508, and 997 are generated in the ionization source 10. The bottom trace of FIG. 7A shows all three of these ions detected and registered as peaks 73, 71, and 74 when the mass spectrometer was in the continuous mode of operation. The top trace mass spectrum in FIG. 7A shows the results *when the mass spectrometer was changed to the ion storage mode of operation*. Both modes were acquired in similar experimental conditions. The acquisition rate i.e. the repetition rate counted by the repeller lens was 8200 per second. Each trace represents 4100 full averaged scans. As seen from the top spectral trace, there is only one predominant registered peak 72 in the spectrum. *This peak corresponds to a molecular ion 508 enhanced in signal strength by about a factor of ten with respect to the peak 71 in continuous mode of operation*. For the reasons explained in above examples, both of the molecular ions 118 and 997 are absent from the ion storage mode spectral trace as expected. The signal intensity increase comes from the fact that all of the ions that would otherwise be lost in the continuous ion mode were actually being stored in the ion guide for the next scan. According to the above example, *for the continuous mode of operation, the approximate duty cycle calculated for the 508 peak at 8,200 scans/s would be 9% i.e. one out of every twelve ions being detected. As the experimental results suggest in the ion storage mode of operation at 8,200 scans/s in FIG. 7A, most of the lost ions predicted in the continuous ion mode were recovered.*

This passag demonstrates an *a molecular ion 508 enhanced.. sign I strength by about a factor of ten with respect to the peak 71 in continuous mode of operation... when the mass spectrometer was changed to the ion storage mode of* operation, that is, as described in the previous passage, by providing a delay between the trap release and the TOF pulse, and adjusting the delay to maximize the intensity of the m/z 508 ion, resulting from an improvement in duty cycle relative to continuous beam operation.

Hence, there is unequivocal support for step (e) in the '259 description only, and even stronger support when considering the included by reference description of '111.

Summary

Count 1 is supported by the description of '259. The support for Count 1 is unequivocal with '259 by itself as well as by the inclusion of '111.

In view of the previously referenced Amendment reply, including the table, the interview conducted on December 9th, the detailed comments herein, and the further review of this application and the related patents which are incorporated into the current application, it is respectfully requested that the Examiner reconsider and withdraw his position that there is insufficient basis to support the count in this projected interference.

Respectfully submitted,

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